EXHIBIT E

High-Fat Foods and the Risk of Lung Cancer

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High-Fat Foods and the Risk of Lung Cancer

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We conducted a population-based case-control study of the association of dietary cholesterol and fat with lung cancer between 1983 and 1985 on Oahu, Hawaii. The study population included 226 men and 100 women with lung cancer, and 597 male and 268 female community controls matched for age (±5 years) and sex. There was a positive dose-response relation between the consumption of processed meats (luncheon meats, bacon, sausage), dairy foods (whole milk, regular ice cream), eggs, and particular desserts (fruit pies, custard/cream pies) and the risk of lung cancer in men. We also found a positive trend in the risk of lung cancer in women with increasing intake of some processed meats (bacon, Spam) and desserts (cakes, custard/cream pies). The dose-response relation tended to be stronger among men who were heavy smokers and who were diagnosed with squamous cell cancer of the lung. A positive trend in risk was found for nitrite intake in men and dimethylnitrosamine intake in men and women. These data indicate that smokers with a high intake of foods rich in fat and animal protein or who have a preference for cured meats are at increased risk of lung cancer. (Epidemiology 1992;3:288–299)

Keywords: cholesterol, diet, fats, lung neoplasms, nitrites, processed meats, tobacco smoking.

During the 1940s, Tannenbaum[1] demonstrated in experimental studies that a high-fat diet could promote cancer. Since that time, the role of dietary fat in cancer causation has been the focus of epidemiologic studies on a number of cancer sites, most notably the breast and colon. More recently, an association of dietary fat and cholesterol with the risk of lung cancer has been examined. Several ecologic studies,[2–4] including one conducted in Hawaii,[5] have shown a positive relation between lung cancer incidence and mortality and the intake of dietary cholesterol and fat. Five case-control studies[6–10] and one cohort study[11] have also shown a positive association between the risk of lung cancer and a diet high in cholesterol or fat.

The high correlation between the various lipid components of the diet hinders interpretation of the association of lipids and disease. In an earlier analysis[8] of data from the present case-control study of lung cancer, we found correlation coefficients for the intakes of cholesterol and fat ranging from 0.54 to 0.78. Thus, it is difficult to separate the effect of cholesterol from that of fat.

Experience has indicated that consumption patterns of foods and food groups may be better predictors of disease incidence than reliance on a single nutrient score. A handful of investigators have examined the effects of specific high-fat foods, such as milk, meat, and eggs, on the risk of lung cancer.[9,11–17] In these studies, however, the focus has generally been on sources of dietary retinol rather than fat.[12–15] The aim of the present analysis is to determine whether particular food sources of dietary cholesterol and fat are associated with lung cancer and to determine whether these associations result from a stronger effect of a particular fatty acid on the risk of this disease.

Subjects and Methods

The methodology used in this study has been described in detail in an earlier paper.[8] The case series for this population-based case-control study in Hawaii comprised all patients with histologically confirmed primary lung cancer diagnosed between March 1, 1983, and September 30, 1985, in one of the seven major civilian hospital centers on Oahu. We identified cases and obtained histologic information through the pathology logs and admission records of the participating hospitals by a rapid-reporting system of the Hawaii Tumor Registry, part of the National Cancer Institute-sponsored Surveillance, Epidemiology, and End Results (SEER) program.[18]

Cases included individuals from 30 to 84 years of

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age who were residents of Oahu and who belonged to one of the five major ethnic groups in Hawaii: Caucasian, Japanese, Chinese, Filipino, and Hawaiian/part-Hawaiian. Completed questionnaires were obtained from 70% (N = 290) of men and 63% (N = 114) of women who were initially eligible for study. Reasons for nonparticipation included physician refusal (5%), patient refusal (5%), language barrier or inability to locate (5%), and death or illness with lack of a suitable surrogate (18%).

Two population-based controls were matched to each case on the basis of sex and 5-year age group. Three different methods were used for control identification. Between April 1983 and July 1984, we used random-digit dialing,[19] creating pools of eligible individuals from which we selected controls. This method proved expensive and labor intensive, so from August 1984 to the end of the study, we selected the remaining controls randomly from lists of Oahu residents who participated in an annual survey, representing a random 2% of households, conducted by the Hawaii Department of Health.[20] The refusal rate for this survey is extremely low (<5%) because it is conducted under statutory provisions. Finally, to supplement the pool of individuals over 65 years of age, we selected additional controls from a 10% random sample of all Oahu residents registered with the Health Care Financing Administration, which has enumerated an estimated 95% of the individuals age 65 and over in the United States.[21] Among controls, interviews were completed for 697 men (71%) and 271 (67%) women who were initially contacted. Reasons for nonparticipation of eligible controls included refusal (19%), inability to locate the subject or language barrier (8%), and death or illness with no available surrogate (3%).

In some instances, the subject had died or was too ill to be interviewed directly. In these circumstances, we obtained surrogate interviews from the spouse or next-of-kin, provided that they had lived with the subject for at least 5 years and considered themselves knowledgeable about the subject's eating habits. Surrogate interviews were conducted for 29% of the cases and 7% of the controls.

All subjects were interviewed in their homes using a structured format for data collection. The questionnaire elicited a detailed diet history, information on the use of vitamin supplements, a lifetime history of tobacco use, and other demographic and anthropometric information. The diet history method has been described previously.[22] In brief, we selected over 130 different food items, along with three serving sizes for each item, that contributed at least 85% of the intakes of cholesterol, fat, vitamin A, and carotene, for individuals in each of the five ethnic groups included in the study. Sources of these nutrients and appropriate serving sizes were based on three-day measured food records from a separate representative sample of 300 men and women who were 45 years of age and older and belonged to the five ethnic groups.[22] We used color photographs illustrating the three most representative serving sizes to assist subjects in estimating amounts consumed. The respondent indicated the usual frequencies consumed per week or month, with yearly frequencies for some seasonal items. Subjects selected amounts of the food items from the pictures in any combination of serving sizes. The reference period was a year before diagnosis or the onset of symptoms for the cases, and during the corresponding time period for the matched controls. Our method has been shown to be reproducible,[23,24] and valid[25] when compared with food record data.

The quantity of each food item consumed on a weekly or monthly basis was calculated as the product of the frequency and serving size. The approach recommended by the Food and Agriculture/World Health Organization Expert Group was used to estimate beta-carotene intake.[26] The consumption of nutrients was computed using food composition data compiled largely from U.S. Department of Agriculture tables[27] and supplemented with other publications.[28–30]

Subjects who smoked pipes and cigars exclusively were not included in the analysis to simplify statistical adjustment for tobacco smoking. We also excluded subjects who had incomplete information on the number of cigarettes smoked or the number of years they had smoked cigarettes. A total of 181 subjects were excluded for these reasons, yielding a final study population of 226 male and 100 female lung cancer cases (representing 56% of the eligible case series), and 597 male and 268 female controls (representing 63% of eligible controls).

We evaluated the risks associated with different levels of the exposure variables using unconditional multiple logistic regression.[31] We divided the combined population of cases and controls into quartiles (or tertiles, in some instances) of food intake (see Appendix for cutpoints). We entered binary indicator variables for the food intake quantiles into the model, with the lowest intake category as the reference group. We also included in the model age (as a continuous variable), ethnicity (using indicator variables), smoking status (never *vs* ever smoked cigarettes), and pack-years of cigarette smoking (number of packs per day ×

number of years smoked). We assigned never-smokers a value of zero pack-years. Ex-smokers were defined as persons who had quit smoking for 3 or more years at the time of the interview. We also adjusted for beta-carotene intake, since this micronutrient was found to be an important protective factor against lung cancer in a previous analysis of these data[32] and was also correlated with fat intake ($r = 0.16$). Alternative adjustment for vegetable intake and the addition of education to the logistic models did not change our findings. We performed a test for linear trend in the logit of risk by comparing twice the difference in log likelihoods for models with and without a trend variable, based on a chi-square distribution with 1 degree of freedom. The trend variables were assigned the values of the medians of the quartiles (or tertiles) of the appropriate food item.

Results

The sociodemographic characteristics of the cases and controls have been described.[8] In brief, the mean age for subjects was 64 years of age. Japanese and Caucasians were the predominant ethnic groups, followed by Hawaiians, Filipinos, and Chinese. Cigarette smoking was much more common among cases (96% of men; 81% of women) than among controls (67% of men; 34% of women).

Table 1 shows odds ratios for lung cancer by quantile of the intake of various fat-containing foods and food groups, after adjustment for covariates. In men, positive, although not always monotonic, trends in the odds ratios were seen with increasing consumption of meats overall and, specifically, processed meats, such as luncheon meats, bacon, and sausage; eggs; dairy foods, including whole milk and ice cream; and desserts, including fruit and custard/cream pies. In women, there were trends in risk associated with increasing intake of Spam and pork, but not meats overall; and desserts, including custard/cream pie and cake. We also found positive dose-response relations for luncheon meats and bacon and the risk of lung cancer in women. Additional adjustment for the intake of cholesterol and total fat, and years of education, as well as alternate adjustment for vegetable intake, did not materially improve the fit of any of the models shown in Table 1.

Odds ratios by the level of intake of the foods listed in Table 1 were generally consistent among the ethnic groups (data not shown). The small number of female lung cancer cases who smoked cigarettes (81) impeded additional analyses on this group. Therefore, we restricted the analyses presented in Tables 2–5 to men. Owing to the large number of food items considered in this analysis, we chose to limit the presentation of our results to those foods showing positive trends in the odds ratios from Table 1.

The risk of lung cancer increases with greater pack-years of cigarette smoking and declines after the cessation of cigarette smoking. To determine whether smoking cessation or pack-years of cigarette use modified the effect of processed meats and other high-fat or animal protein foods on the odds ratios for lung cancer among men, we analyzed the dietary data separately for current and past smokers and for two cigarette smoking levels among ever-smokers: less than or equal to 40 pack-years and greater than 40 pack-years. Although there was only minor variation in the effect of food consumption on the odds ratios for lung cancer by cigarette smoking history, in general, the results were a little stronger for the current smokers than the past smokers (Table 2). Although odds ratios were generally higher with greater consumption of foods high in fat or animal protein among both light (≤40 pack-years) and heavy (>40 pack-years) smokers, trends tended to be stronger and more frequently monotonic among the smokers with a longer pack-year history (Table 3).

Histologic-specific analyses of the data for men indicated a stronger relation of food consumption patterns to the risk of squamous cell lung cancer than to the risk of adenocarcinoma of the lung (Table 4). Monotonic dose-response relations between food intake and the odds ratios for squamous cell lung cancer were found for all meat and processed meats (luncheon meats, bacon, sausage), dairy foods, ice cream, and desserts. Only a few strong, positive trends were found in the risk of adenocarcinoma of the lung and food consumption: these were limited to bacon, sausage, and ice cream. Too few subjects (34) had small cell lung cancer to permit a separate analysis.

The results from Tables 2 and 4 indicate that the association of dietary fat and animal protein with lung cancer risk in this study is stronger among men with squamous cell lung cancer who were current smokers at the time of the interview. Therefore, for this subgroup only, regression models were created with five dummy variables: one representing the main effect for the dietary variables (based on dichotomization at the median), two representing the main effects for pack-years (≤40, 41–70, >70), and two representing interaction terms. Current smokers with a smoking history of less than or equal to 40 pack-years and low food intake were used as the reference category. The results for sausage and dairy food intakes are shown

TABLE 1. Odds Ratios* and 95% Confidence Intervals (CI) for Lung Cancer by Quantile (Q) of Intake of Selected Food Items

	Men (226 Cases, 597 Controls)				Women (100 Cases, 268 Controls)			
	Odds Ratios (95% CI)			P	Odds Ratios (95% CI)			P
Food or Food Group	Q2 *vs* Q1	Q3 *vs* Q1	Q4 *vs* Q1	for Trend	Q2 *vs* Q1	Q3 *vs* Q1	Q4 *vs* Q1	for Trend
All meat	1.0 (0.6–1.9)	1.8 (1.0–3.2)	1.7 (0.9–3.0)	0.03	0.9 (0.4–1.9)	2.0 (0.9–4.5)	0.8 (0.2–2.4)	0.52
Processed meat								
Luncheon meat	1.1 (0.6–1.8)	1.5 (0.9–2.5)	1.7 (1.1–2.8)	0.01	1.2 (0.6–2.6)	2.5 (1.1–5.8)	2.0 (0.8–4.8)	0.07
Bacon	2.1 (1.3–3.5)	1.5 (0.9–2.5)	2.9 (1.8–4.6)	0.002	1.4 (0.7–3.0)	1.2 (0.6–2.6)	2.7 (1.1–6.5)	0.06
Sausage	1.6 (0.9–2.9)	1.6 (0.9–2.9)	3.4 (2.0–6.0)	0.0008	1.3 (0.6–2.7)	1.2 (0.5–2.7)	1.3 (0.5–3.2)	0.62
Ham	1.3 (0.8–2.0)	0.8 (0.5–1.3)		0.32	1.2 (0.6–2.4)	1.4 (0.6–2.8)		0.43
Bologna	1.5 (1.0–2.1)				1.3 (0.7–2.6)			
Spam	1.0 (0.7–1.6)	1.4 (0.9–2.1)		0.12	2.1 (1.0–4.3)	2.5 (1.0–6.2)		0.04
Fresh meat								
Ground beef	1.3 (0.8–2.2)	1.3 (0.8–2.3)	1.0 (0.6–1.8)	0.68	1.1 (0.5–2.4)	1.3 (0.6–2.9)	0.9 (0.3–2.5)	0.89
Beef stew	0.9 (0.6–1.6)	0.9 (0.5–1.4)	0.9 (0.5–1.4)	0.65	1.6 (0.8–3.6)	1.6 (0.8–3.6)	1.4 (0.5–3.5)	0.70
Other beef	1.9 (1.1–3.3)	1.4 (0.8–2.5)	1.2 (0.7–2.2)	0.68	1.4 (0.7–3.0)	0.8 (0.3–1.8)	0.9 (0.4–2.3)	0.62
Pork	1.8 (1.2–2.8)	1.4 (0.9–2.2)		0.22	1.9 (0.9–3.8)	2.6 (1.2–5.6)		0.02
Lamb	1.1 (0.4–2.7)				1.0 (0.3–3.4)			
Liver	1.2 (0.7–1.9)	1.6 (1.0–2.4)		0.06	1.4 (0.7–3.0)	1.0 (0.4–2.3)		0.96
Poultry	0.6 (0.4–1.0)	0.6 (0.4–1.0)	0.7 (0.5–1.1)	0.41	0.5 (0.2–1.3)	0.6 (0.3–1.4)	0.5 (0.2–1.3)	0.14
Chicken	0.7 (0.4–1.2)	0.8 (0.5–1.2)	0.7 (0.4–1.1)	0.16	0.7 (0.3–1.5)	0.7 (0.3–1.5)	0.7 (0.3–1.5)	0.34
Duck	1.6 (1.0–2.6)				1.8 (0.7–4.9)			
Fish	1.4 (0.8–2.3)	1.2 (0.7–2.0)	1.2 (0.7–2.0)	0.87	0.6 (0.3–1.3)	1.0 (0.4–2.2)	0.5 (0.2–1.4)	0.32
Lean	1.3 (0.8–2.2)	0.8 (0.5–1.4)	1.0 (0.6–1.5)	0.84	1.0 (0.5–2.1)	0.4 (0.2–1.0)	0.6 (0.3–1.7)	0.16
Shellfish	1.4 (0.9–2.1)	1.0 (0.6–1.5)		0.80	1.2 (0.6–2.4)	1.3 (0.6–3.0)		0.47
Canned fish	0.6 (0.4–1.0)	0.9 (0.6–1.3)		0.91	1.3 (0.6–2.7)	1.1 (0.5–2.3)		0.86
Shrimp	1.5 (1.0–2.2)	0.8 (0.5–1.3)		0.36	1.4 (0.7–2.7)	1.4 (0.5–3.8)		0.40
Eggs	0.8 (0.5–1.4)	1.0 (0.6–1.6)	1.5 (0.9–2.4)	0.02	1.2 (0.6–2.6)	1.2 (0.5–2.7)	0.8 (0.3–2.0)	0.58
Dairy foods	1.1 (0.7–1.9)	1.9 (1.1–3.2)	2.4 (1.4–4.0)	0.002	0.6 (0.2–1.3)	0.5 (0.2–1.3)	1.7 (0.7–4.0)	0.32
Whole milk	0.8 (0.5–1.3)	2.1 (1.3–3.3)		0.006	1.5 (0.7–3.3)	2.0 (0.9–4.2)		0.10
Low-fat milk	0.6 (0.3–1.0)	0.9 (0.5–1.6)		0.72	0.6 (0.2–1.6)	1.3 (0.6–2.9)		0.52
Ice cream	1.2 (0.7–2.0)	1.4 (0.9–2.3)	2.3 (1.5–3.7)	0.0009	1.6 (0.7–3.4)	1.3 (0.6–3.0)	1.5 (0.6–3.4)	0.42
Cheese	1.2 (0.7–1.9)	1.5 (0.9–2.3)	0.9 (0.5–1.6)	0.53	1.4 (0.7–2.7)	1.4 (0.7–2.8)	1.0 (0.5–2.3)	0.61
Fried foods	1.4 (0.8–2.4)	1.8 (1.1–3.1)	1.4 (0.8–2.4)	0.39	1.5 (0.7–3.2)	1.5 (0.7–3.5)	1.5 (0.6–3.9)	0.48
Fats and oils								
Butter	1.0 (0.6–1.7)	1.4 (0.8–2.3)		0.23	1.0 (0.4–2.6)	1.2 (0.5–3.0)		0.73
Margarine	1.0 (0.6–1.7)	1.4 (0.8–2.2)	1.1 (0.7–1.8)	0.66	1.1 (0.5–2.5)	0.8 (0.3–1.8)	1.0 (0.5–2.3)	0.99
Peanut butter	0.9 (0.6–1.4)	0.7 (0.4–1.1)		0.10	1.4 (0.7–2.7)	0.8 (0.4–1.7)		0.45
Oil	1.1 (0.6–1.8)	1.2 (0.7–2.1)	1.5 (0.9–2.6)	0.07	0.7 (0.3–1.6)	1.4 (0.6–3.2)	1.1 (0.4–2.6)	0.61
Mayonnaise	1.8 (1.1–2.9)	1.5 (0.9–2.4)	1.5 (0.9–2.4)	0.45	1.1 (0.5–2.5)	1.2 (0.5–2.6)	1.6 (0.7–3.5)	0.28
Nuts and chips								
Potato and corn chips	0.9 (0.6–1.4)	0.9 (0.6–1.4)		0.63	0.7 (0.3–1.7)	1.2 (0.6–2.6)		0.52
Peanuts	1.0 (0.6–1.7)	1.1 (0.7–1.6)		0.66	1.2 (0.5–2.6)	0.8 (0.3–2.0)		0.66
Desserts	1.2 (0.8–2.0)	1.2 (0.7–1.9)	1.8 (1.1–2.9)	0.01	1.1 (0.5–2.4)	1.1 (0.5–2.5)	3.3 (1.5–7.5)	0.0009
Fruit pie	1.4 (0.9–2.3)	1.6 (1.1–2.4)		0.02	0.8 (0.3–1.8)	1.6 (0.7–3.6)		0.33
Custard or cream pie	1.0 (0.6–1.7)	1.9 (1.2–2.9)		0.006	1.2 (0.4–3.2)	3.0 (1.3–7.4)		0.01
Cakes	1.3 (0.8–2.1)	1.1 (0.7–1.8)		0.76	1.1 (0.5–2.5)	2.2 (1.0–4.9)		0.04
Other								
Avocado	1.1 (0.6–1.8)	1.0 (0.6–1.5)	0.8 (0.5–1.3)	0.38	1.8 (0.8–4.2)	1.3 (0.6–3.0)	1.6 (0.7–3.6)	0.57

* Adjusted by multiple logistic regression for age, ethnicity, smoking status, pack-years of cigarette use, and beta-carotene intake.

for illustrative purposes in Table 5. Within each level of smoking, there was an increased risk of squamous cell lung cancer associated with a high intake of sausage and dairy foods. Current smokers with a history of more than 70 pack-years who were high dairy consumers had 38 times the risk of squamous cell lung cancer compared with men with a history of 40 pack-years or less who were low consumers.

TABLE 2. Odds Ratios* and 95% Confidence Intervals (CI) for Lung Cancer among Men by Quartile (Q) of Intake of Selected Food Items and Cigarette Smoking History†

Food or Food Group	Current Smoker (148 Cases, 169 Controls)				Past Smoker (68 Cases, 229 Controls)			
	Odds Ratios (95% CI)			*P* for Trend	Odds Ratios (95% CI)			*P* for Trend
	Q2 *vs* Q1	Q3 *vs* Q1	Q4 *vs* Q1		Q2 *vs* Q1	Q3 *vs* Q1	Q4 *vs* Q1	
All meat	1.2 (0.5–3.0)	1.7 (0.7–4.2)	1.7 (0.7–4.3)	0.14	0.9 (0.3–2.3)	1.6 (0.6–3.9)	1.2 (0.5–3.2)	0.39
Luncheon meat	0.7 (0.3–1.4)	0.9 (0.4–1.9)	1.3 (0.7–2.5)	0.13	1.5 (0.7–3.6)	2.8 (1.2–6.2)	2.1 (0.9–4.8)	0.11
Bacon	2.5 (1.1–5.4)	1.6 (0.8–3.2)	2.5 (1.3–4.8)	0.04	2.0 (1.0–4.4)	1.1 (0.4–2.6)	2.4 (1.1–5.2)	0.08
Sausage	1.1 (0.5–2.7)	1.1 (0.5–2.4)	2.5 (1.1–5.6)	0.004	1.4 (0.6–3.6)	1.7 (0.7–4.4)	2.9 (1.2–7.1)	0.01
Eggs	0.9 (0.4–2.0)	1.0 (0.5–2.2)	1.7 (0.8–3.4)	0.05	0.8 (0.4–1.8)	0.7 (0.3–1.8)	1.0 (0.4–2.2)	0.85
Dairy foods	1.2 (0.6–2.4)	2.3 (1.1–4.9)	2.8 (1.3–6.3)	0.0001	1.3 (0.6–3.0)	1.5 (0.6–3.7)	2.1 (0.9–5.1)	0.09
Ice cream	1.0 (0.5–1.9)	1.4 (0.7–2.6)	1.7 (0.9–3.4)	0.07	1.3 (0.6–2.9)	1.2 (0.5–2.6)	2.4 (1.1–5.1)	0.03
Desserts	1.3 (0.6–2.6)	1.1 (0.5–2.1)	1.4 (0.7–2.7)	0.38	1.1 (0.5–2.6)	1.2 (0.5–2.9)	1.9 (0.9–4.1)	0.07

* Adjusted by multiple logistic regression for age, ethnicity, pack-years of cigarette use, and beta-carotene intake.
† Current smoker: current smoker or ex-smoker for up to 2 years before interview; past smoker: ex-smoker for 3 or more years.

TABLE 3. Odds Ratios* and 95% Confidence Intervals (CI) for Lung Cancer among Men by Quartile (Q) of Intake of Selected Food Items and Pack-Years of Cigarette Consumption among Ever-Smokers

Food or Food Group	≤40 Pack-Years (54 Cases, 207 Controls)				>40 Pack-Years (162 Cases, 191 Controls)			
	Odds Ratios (95% CI)			*P* for Trend	Odds Ratios (95% CI)			*P* for Trend
	Q2 *vs* Q1	Q3 *vs* Q1	Q4 *vs* Q1		Q2 *vs* Q1	Q3 *vs* Q1	Q4 *vs* Q1	
All meat	1.9 (0.6–6.0)	1.7 (0.6–5.5)	1.5 (0.4–4.7)	0.89	0.7 (0.3–1.7)	1.5 (0.7–3.4)	1.5 (0.7–3.3)	0.04
Luncheon meat	1.0 (0.3–2.7)	2.0 (0.8–4.9)	1.6 (0.7–4.0)	0.22	1.0 (0.6–2.0)	1.6 (0.8–2.9)	1.9 (1.1–3.5)	0.02
Bacon	2.2 (0.9–5.1)	1.6 (0.6–3.8)	2.4 (0.9–6.1)	0.17	2.3 (1.1–4.6)	1.5 (0.8–3.0)	2.7 (1.5–4.8)	0.005
Sausage	1.5 (0.5–4.2)	0.8 (0.3–2.3)	1.5 (0.5–4.0)	0.44	1.3 (0.6–2.9)	2.0 (1.0–4.2)	4.6 (2.3–9.3)	0.0001
Eggs	0.7 (0.3–1.9)	0.6 (0.3–1.6)	0.6 (0.3–1.6)	0.42	0.8 (0.4–1.7)	1.2 (0.6–2.3)	2.2 (1.2–4.3)	0.006
Dairy foods	1.2 (0.5–3.1)	1.3 (0.5–3.7)	1.5 (0.5–4.2)	0.55	1.2 (0.6–2.2)	2.8 (1.4–5.6)	3.4 (1.6–6.9)	0.0001
Ice cream	1.5 (0.6–3.5)	1.3 (0.5–3.0)	1.5 (0.6–3.8)	0.50	0.9 (0.5–1.7)	1.6 (0.8–3.0)	2.4 (1.3–4.3)	0.008
Desserts	1.0 (0.4–2.5)	1.1 (0.4–2.8)	2.4 (1.0–6.0)	0.02	1.2 (0.6–2.2)	1.3 (0.6–2.4)	1.4 (0.8–2.5)	0.29

* Adjusted by multiple logistic regression for age, ethnicity, pack-years of cigarette use, and beta-carotene intake.

TABLE 4. Odds Ratios* and 95% Confidence Intervals (CI) for Lung Cancer among Men by Tertile (T) of Intake of Selected Food Items and Histologic Type

Food or Food Group	Squamous Cell (77 Cases, 597 Controls)			Adenocarcinoma (85 Cases, 597 Controls)		
	Odds Ratios (95% (CI)			Odds Ratios (95% CI)		
	T2 *vs* T1	T3 *vs* T1	*P* for Trend	T2 *vs* T1	T3 *vs* T1	*P* for Trend
All meat	1.2 (0.5–2.8)	2.4 (1.1–5.2)	0.003	1.4 (0.7–2.7)	1.4 (0.7–2.8)	0.44
Luncheon meat	2.0 (0.9–4.5)	3.2 (1.6–6.8)	0.0004	0.8 (0.4–1.6)	1.4 (0.8–2.4)	0.15
Bacon	1.8 (0.9–3.8)	3.1 (1.6–6.0)	0.0008	2.2 (1.1–4.4)	3.7 (2.0–7.1)	0.0002
Sausage	2.4 (1.0–5.8)	5.7 (2.5–13.0)	0.0001	1.6 (0.8–3.1)	2.4 (1.2–4.6)	0.01
Eggs	0.7 (0.4–1.5)	1.7 (0.9–3.1)	0.02	1.4 (0.8–2.7)	1.2 (0.7–2.3)	0.80
Dairy foods	2.4 (1.1–5.1)	4.6 (2.2–9.9)	0.0001	1.8 (1.0–3.2)	1.3 (0.7–2.5)	0.76
Ice cream	1.4 (0.8–2.7)	2.4 (1.2–4.5)	0.01	1.1 (0.6–2.0)	2.5 (1.4–4.6)	0.008
Desserts	1.5 (0.7–3.0)	2.4 (1.2–4.5)	0.002	1.5 (0.8–2.7)	1.1 (0.6–2.1)	1.00

* Adjusted by multiple logistic regression for age, ethnicity, smoking status, pack-years of cigarette use, and beta-carotene intake.

TABLE 5. Odds Ratios* and 95% Confidence Intervals (CI) for Squamous Cell Lung Cancer among Male Current Smokers,† by Pack-Years of Cigarette Smoking and by Sausage and Dairy Food Consumption

	Sausage Consumption‡				Dairy Food Consumption‡			
	Low (12 Cases, 55 Controls)		High (42 Cases, 97 Controls)		Low (15 Cases, 94 Controls)		High (39 Cases, 58 Controls)	
Pack-Years	Odds Ratio	(95% CI)	Odds Ratio	(95% CI)	Odds Ratio	(95% CI)	Odds Ratio	(95% CI)
≤40	1.0§		1.2	(0.2–6.1)	1.0§		8.6	(1.7–42.8)
41–70	1.6	(0.3–9.5)	3.7	(0.8–16.9)	5.0	(1.2–21.3)	13.7	(3.0–63.9)
>70	3.6	(0.6–22.3)	11.8	(2.3–61.6)	4.0	(0.5–29.6)	38.2	(8.2–178.6)

* Adjusted by multiple logistic regression for age and ethnicity. Chinese males were excluded from these analyses because of the small number (N = 3) of cases.
† Current smoker: current smoker or ex-smoker for up to 2 years.
‡ Based on dichotomization at the median intake value.
§ Reference category.

Inasmuch as processed meats are a major dietary source of nitrite and, to a lesser extent, nitrosamines,[33] Table 6 shows the association of these micronutrients with the odds ratios for lung cancer. Among men, a positive monotonic trend in the odds ratios for lung cancer was found for nitrite and dimethylnitrosamine intake. In women, a positive dose-response relation was shown for dimethylnitrosamine intake, but not for nitrite. As expected, nitrate consumption was inversely related to the risk of lung cancer in men and women (data not shown), since vegetable intake, found to be a strong protective factor in an earlier analysis of these data,[32] contributes about 86% of the daily intake of this micronutrient.[33]

Discussion

We found strong, positive, dose-response relations for lung cancer among both men and women for the consumption of a number of foods that are high in fat, such as meat items, dairy foods, and desserts (cakes and pies). There are several ways in which an excess of fat in the diet may promote (or initiate) lung carcinogenesis. Dietary fat and cholesterol play an integral role in the immune function of cells. Cell membrane lipid composition affects cellular fluidity and permeability[34,35] and is also important to gap-junctional communication.[36] Phagocytosis by macrophages *in vitro* is inhibited by the alteration of cellular cholesterol and polyunsaturated fatty acid composition.[37] Finally, prostaglandins may act as immunosuppressants through the inhibition of lymphocyte cytotoxicity and may also modulate cell proliferation.[38]

Although it is difficult to separate the effects of cholesterol and the various fatty acids in dietary studies due to the high collinearity among these nutrients, this analysis indicates that the association of fat and lung cancer is restricted to fat from animal sources, especially processed meats, in agreement with the international ecologic study of Xie *et al.*[4] The consumption of oil, margarine, peanut butter, peanuts, and avocado, which are free of cholesterol and low in saturated fat, was not related to the odds ratios for lung cancer. Lung cancer was also not related to the intake of shrimp, which contains cholesterol but is low in fat. In spite of the differences in risk associated with various sources of dietary fat, on the basis of this analysis, it is still difficult to draw any specific conclusions regarding an independent role for cholesterol or fat in the development of lung cancer.

It is of interest that the risk of lung cancer was not increased among people favoring fried foods in their diet. Frying at high temperatures leads to a greater rate of fatty acid oxidation and may increase the rate of tissue damage through the production of free radicals,

TABLE 6. Odds Ratios* and 95% Confidence Intervals (CI) for Lung Cancer by Quartile (Q) of Intake of Nitrite and Dimethylnitrosamine

	Men (226 Cases, 597 Controls)				Women (100 Cases, 268 Controls)			
	Odds Ratios (95% CI)				Odds Ratio (95% CI)			
Nutrient	Q2 *vs* Q1	Q3 *vs* Q1	Q4 *vs* Q1	*P* for Trend	Q2 *vs* Q1	Q3 *vs* Q1	Q4 *vs* Q1	*P* for Trend
Nitrite	1.2 (0.6–2.3)	1.7 (0.9–3.3)	2.0 (1.0–3.8)	0.02	0.6 (0.2–1.2)	0.9 (0.4–2.1)	1.5 (0.5–4.1)	0.22
Dimethylnitrosamine	1.7 (0.9–3.2)	2.8 (1.4–5.3)	3.3 (1.7–6.2)	0.0006	1.4 (0.7–2.9)	1.8 (0.7–4.2)	2.7 (1.0–6.9)	0.04

* Adjusted by multiple logistic regression for age, ethnicity, smoking status, pack-years of cigarette use, and beta-carotene intake.

TABLE 7. Dietary Fat and Cholesterol and Lung Cancer Risk: A Summary of Case-Control and Cohort Studies

Author(s), Year of Publication, Reference No.	Study Design; Place	Study Population	Diet Measurement Method	Nutrient or Food	Nutrient or Food Level	Relative Risk			Comment
						Males	Females	Total	
Mettlin *et al*, 1979[12]	Case-control; New York	291 male cases 801 hospital controls	Food frequency questionnaire of 45 foods and beverages	Milk	Lowest 1	1.6			Strong inverse association of milk intake and the risk of lung cancer in men. No attempt made to analyze the data by fat content of milk.
					Highest 2	1.0			
Hinds *et al*, 1983[6]	Case-control; Hawaii	364 cases 627 community controls	Quantitative food frequency questionnaire of 84 foods and beverages	Cholesterol	Lowest 1	1.0	1.0		Monotonic, positive dose-response relationship between dietary cholesterol and lung cancer risk in all subjects, smoking subjects, and men. No association found for women.
					2	1.2	1.7		
					3	1.4	1.3		
					Highest 4	2.3	1.2		
Wu *et al*, 1985[13]	Case-control; Los Angeles	220 female cases 220 community controls	Food frequency questionnaire of 28 foods and beverages	Dairy products and eggs	Lowest 1		2.7		Inverse association of intake of dairy products (cheese, butter, margarine, cream, milk) and eggs and the risk of lung cancer in females.
					2		2.2		
					3		1.7		
					Highest 4		1.0		
Byers *et al*, 1987[7]	Case-control; New York	450 cases 902 community controls	Semiquantitative food frequency questionnaire of 129 foods and beverages	Total fat	Lowest 1	0.5	0.7		Weak positive association between dietary fat and cholesterol intake and the risk of lung cancer for men. Males in the lowest quartile of fat intake were at significantly decreased risk.
					2	0.8	1.3		
					3	0.9	0.7		
					Highest 4	1.0	1.0		
				Cholesterol	Lowest 1	0.7	1.1		
					2	0.9	1.7		
					3	1.2	1.2		
					Highest 4	1.0	1.0		
Goodman *et al*,* 1988[8]	Case-control; Hawaii	326 cases 865 community controls	Quantitative food frequency questionnaire of >130 foods and beverages	Total fat	Lowest 1	1.0	1.0		Strong positive association of dietary fat and cholesterol and the risk of lung cancer in men, but not women. Effect in men stronger in current smokers who smoked heavily and in squamous and small cell histologic types.
					2	2.3	0.4		
					3	2.0	0.8		
					Highest 4	2.2	0.9		
				Cholesterol	Lowest 1	1.0	1.0		
					2	2.3	0.6		
					3	1.8	1.5		
					Highest 4	2.2	0.9		
Mettlin 1989[9]	Case-control; New York	569 cases 569 hospital controls	Food frequency questionnaire of 45 foods and beverages	Animal fat	Lowest 1			1.0	Weak positive association of dietary fat and the risk of lung cancer in both sexes combined. Positive gradient of risk for whole milk, pork chops, as well as ham and pork sausage (data not shown).
					2			1.3	
					3			1.4	
					4			1.5	
					Highest 5			1.5	
				Whole milk	Lowest 1			1.0	
					2			1.6	
					3			1.6	
					Highest 4			2.1	
				Pork chops	Lowest 1			1.0	
					2			1.3	
					3			1.5	
					Highest 4			2.4	

TABLE 7. Continued

Jain *et al*, 1990[10]	Case-control; Canada	839 cases 772 community controls	Quantitative food frequency questionnaire of 81 foods and beverages	Cholesterol	Lowest 1 Highest 2	1.0 1.4	1.0 1.7	Strong positive trend for total cholesterol intake (data not shown). Cholesterol effect is strongest for adenocarcinoma of the lung.
				Total fat	Lowest 1 Highest 2		1.0 1.3	
Kvåle *et al*, 1983[15]	Prospective cohort; Norway	168 male cases 16,545 noncases	28-day food frequency questionnaire of 31 food items and beverages	Milk	Lowest 1 Highest 4	1.0 0.3		Strong inverse association found for milk intake and the risk of squamous cell and small cell cancers (based on 50 cases).
				Meat	Lowest 1 Highest 4	1.0 1.0		
				Eggs	Lowest 1 Highest 4	1.0 0.9		
Heilbrun *et al*, 1984[16]	Prospective cohort; Hawaii	109 Japanese male cases 7,420 noncases	24-hour semiquantitative food frequency questionnaire of 54 foods and beverages	Cholesterol	Lowest 1 2 3 Highest 4	1.0 0.7 1.0 1.0		No association found for cholesterol intake, even for subgroups of stage and histologic type.
Shekelle *et al*, 1991[11]	Prospective cohort; Illinois	57 male cases 1,821 noncases	28-day semiquantitative food frequency questionnaire of 195 foods and beverages	Cholesterol	Lowest 1 2 Highest 3	1.0 1.3 1.9		Strong positive trend for total cholesterol intake. Association specific to consumption of cholesterol in eggs.
Fraser *et al*, 1991[17]	Prospective cohort; California	61 cases 34,137 noncases	Food frequency questionnaire of 51 foods and beverages	Meat, fish, or poultry	Lowest 1 2 Highest 3		1.0 1.9 1.3	No association found for combined consumption of meat, fish, and poultry, or milk intake.
				Milk	Lowest 1 2 Highest 3		1.0 1.0 0.9	

* Presently analyzed data.

polycyclic aromatic hydrocarbons, and several other chemical derivatives.[39]

The strong association of processed meats, such as luncheon meats, bacon, and sausage, with the risk of lung cancer is intriguing. Cured meats are a major source of nitrite in the U.S. diet.[33] Dimethylnitrosamines may be ingested through tobacco smoke or alcohol, as well as cured meat, or may be formed endogenously through the nitrosation of secondary amines by nitrites.[40] *N*-nitroso compounds have been shown to be mutagens and important carcinogens for a number of target organs, such as the liver, stomach, brain, and lung.[33] In this analysis, we found a strong relation between consumption of nitrite in men, and dimethylnitrosamines in men and women, and the risk of lung cancer. Nevertheless, the relation of nitrosamines to the risk of lung cancer probably only provides a partial explanation for the association of cured meats with this malignancy, since other foods found to be risk factors, such as dairy products and desserts, contain very low levels of nitrite and negligible amounts of nitrosamines.[41]

Consistent with our previous report on dietary cholesterol, but not with the findings of Jain *et al*,[10] we found that the consumption of foods high in fat was more strongly associated with the risk of squamous cell cancer of the lung than with adenocarcinoma. Although there was some variation in the effects of specific fat-containing foods and food groups on the risk of lung cancer between subgroups of current and past smokers, there was more evidence for heterogeneity in the odds ratios by pack-years of cigarette use: dose-response relations tended to be stronger among heavy smokers than light smokers.

Results from a previous analysis of these data[8] and an earlier case-control study conducted by our group[6] indicated a relation of cholesterol and fat to lung cancer among men, but not women. The present analysis shows greater consistency in the results for men and women, especially for certain meats, whole milk, and desserts. This homogeneity in our results by sex is in accord with the findings of the Canadian case-control study by Jain *et al*.[10] In the absence of a biological explanation for a difference in the association of fat and lung cancer between men and women, we postulated that the lack of an effect of cholesterol on lung cancer among women may have been a result of the smaller proportion of squamous cell lung cancers in females compared with males. There were too few squamous cell cancers (22) in women to conduct a sex-specific analysis of foods by histologic type.

Although the reports from case-control and cohort studies have not been completely consistent, there is mounting evidence from recent investigations for a positive association between dietary sources of fat and cholesterol and the risk of lung cancer (Table 7). Mettlin[9] showed a positive association of dietary fat with lung cancer in both sexes combined. An increased risk of lung cancer was associated with consumption of certain sources of animal fat, including whole milk, pork chops, pork sausage, and ham. Hinds *et al*[6] reported a monotonic dose-response relation for the association of dietary cholesterol and lung cancer among men, but not women. Byers *et al*[7] found a weak positive trend in the association of cholesterol and fat intake and the development of lung cancer: men in the lowest quartile of fat intake were at decreased risk of lung cancer. Jain *et al*.[10] reported an elevated risk of lung cancer associated with high cholesterol and fat intake. The effect was similar for smokers and nonsmokers and for men and women. Most recently, Shekelle *et al*[11] investigated the association of cholesterol intake and lung cancer incidence among men in the Chicago Western Electric Study and found a positive trend in the rate for lung cancer by total cholesterol consumption, which appeared to be specific to cholesterol from eggs.

In this study, selection of incident cases reduced the potential for making erroneous conclusions if either survival or participation in the study were related to dietary patterns or exposure to other risk factors of interest. The response rates for cases and controls compare favorably with other studies of this kind.[7,10] We have focused considerable attention on validating our dietary instrument, and results have shown good agreement of our diet history method with food records.[25] Unfortunately, because of the rapidly lethal nature of lung cancer, 29% of eligible patients died before we could interview them. We used surrogate respondents in this study to ensure the representativeness of the study subjects. In an earlier study, we showed that dietary information from spouses was reasonably valid.[42] Furthermore, we found that the results of the main analyses presented here that were based on direct interviews only were in excellent agreement with results based on the entire dataset. There is a strong association between cigarette smoking and the risk of lung cancer, and tobacco use is also related to dietary patterns.[43,44] In earlier analyses of these data,[8,32] we discussed the possibility of biased estimates of risk resulting from residual confounding due to smoking. To minimize this source of bias, we gathered detailed information on tobacco smoking and adjusted for smoking in all of our analyses.

These results show that analyses of the association of specific foods and food groups with lung cancer risk may have some advantages over the analysis of macronutrients. For example, the positive association of certain foods with the risk of lung cancer among women was missed in our analysis of nutrients alone.[8] The importance of animal sources rather than vegetable sources of fat to the development of lung cancer was also more apparent in the present analysis.

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APPENDIX

Quartile and Tertile Cutpoints for the Intake of Foods, Food Groups (Grams/Week), and Nutrients (Micrograms/Week) by Study Subjects in a Lung Cancer Case-Control Study

Food, Food Group, or Nutrient	Quartile Cutpoints (Upper Bound)			Tertile Cutpoints (Upper Bound)	
	1	2	3	1	2
All meat*	430	820	1,230	560	1,100
Processed meat					
Luncheon meat	0	30	85	5	55
Bacon	0	7	22	0	15
Sausage	15	55	125	30	100
Ham				0	24
Bologna		(Never, ever)			
Spam				0	30
Fresh meat					
Ground beef	23	96	186		
Beef stew	0	83	166		
Other beef	65	140	265		
Pork				0	36
Lamb		(Never, ever)			
Liver				0	28
Poultry	85	140	255		
Chicken	65	120	235		
Duck		(Never, ever)			
Fish	75	165	310		
Lean	40	100	200		
Shellfish				0	30
Canned fish				0	35
Shrimp				0	21
Eggs	49	106	210	68	175
Dairy foods	160	550	1,480	260	1,030
Whole milk				0	718
Low-fat milk				0	828
Ice cream	0	60	239	0	130
Cheese	0	28	87		
Fried foods	35	85	175		
Fats and oils					
Butter				0	28
Margarine	0	20	67		
Peanut butter				0	14
Oil	9	21	40		
Mayonnaise	0	13	43		

APPENDIX. Continued

Food, Food Group, or Nutrient	Quartile Cutpoints (Upper Bound)			Tertile Cutpoints (Upper Bound)	
	1	2	3	1	2
Nuts and chips					
Potato and corn chips				0	14
Peanuts				0	33
Desserts	0	55	145	15	105
Fruit pie				0	54
Custard or cream pie				0	35
Cake				0	28
Other					
Avocado	0	9	35		
Nitrite	2,000	4,000	7,000		
Dimethylnitrosamine	0.07	0.35	0.70		

* All meat includes processed meat and fresh meat.